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Dated 8 July 2003

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P01/7700 0.00-0218781.3

Patents Form 1/77

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1/77

Request for grant of a patent

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The Patent Office

Cardiff Road
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1. Your reference — 100810

2. Patent application number *(The Patent Office will fill in this part)* — 0218781.3 — 13 AUG 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
S-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — Sweden — 7822448003

4. Title of the invention

CHEMICAL PROCESS

5. Name of your agent *(if you have one)*

Dr Anne Williams

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG

Patents ADP number *(if you know it)* — 7822471002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

I ents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	7
Claim(s)	2 DM
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date Authorised Signatory 12/08/2002

12. Name and daytime telephone number of person to contact in the United Kingdom: Jennifer C Bennett - 01625 230148

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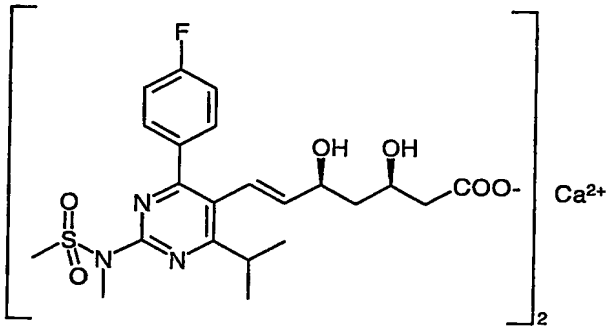
CHEMICAL PROCESS

This invention concerns improvements to a chemical process, particularly a chemical process for manufacture of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt (illustrated below), which is useful for the production of a pharmaceutical useful in the treatment of, inter alia, hypercholesterolemia, hyperlipoproteinemia and atherosclerosis.



Compound (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid (hereinafter referred to as the 'Agent') and its sodium salt and calcium salt were disclosed in European Patent 0521471. This patent also describes a process for the synthesis of the calcium salt of the Agent, the final stage of which is the conversion of the sodium salt of the Agent into the calcium salt. The calcium salt thus formed is then collected and dried and may be processed further as required.

This conversion of the sodium salt into the calcium salt, followed by collection and drying is also described in our International Patent Application WO 00/49014.

The process as described in both of the above documents comprises dropwise addition of an aqueous solution of calcium chloride to an aqueous solution of the sodium salt at 20°C, stirring of the resulting mixture for, for example 45 minutes, and then isolation of the product precipitate by filtration. The filtered product is washed and dried under reduced pressure at 40°C. Efficient washing of the product is essential to ensure removal of sodium chloride produced as a by-product of the reaction. Filtration and drying are then required to give a final product suitable for use as a pharmaceutical.

Precipitation at 20°C according to the process described in these applications produces a product which has a physical form such that it is difficult and slow (ie inefficient) to filter,

and retains a substantial quantity of water after filtration. This necessitates extensive drying in order to obtain a final product suitable for use as a pharmaceutical. Although manageable on a small (laboratory) or medium scale, on a manufacturing scale, handling a product requiring such treatment is highly problematic and is undesirable in terms of manufacturing output and, potentially, product quality.

We have discovered a surprising improvement to the process of manufacturing the calcium salt, which results in improved efficiency of filtration of the product during the isolation process.

In general, reference to improved efficiency of filtration refers to achieving removal of more solvent, such as water, from the product during filtration and optionally to filtration being faster. It will be appreciated that in general a product which is isolated with a low solvent (such as water) content requires less drying time after isolation than one with a higher solvent content in order to achieve the same overall endpoint. It will also be appreciated that the advantages associated with efficient filtration during the initial isolation of the product will also be realised for filtrations carried out as part of any subsequent washing process.

It will be appreciated therefore that the process of the current invention results in significant manufacturing advantages, for example increased manufacturing output.

Accordingly, the present invention provides an improved process for the manufacture of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, which process comprises mixing of a solution of calcium chloride with a solution of a water-soluble salt of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid, wherein the process parameters are selected to give a product which demonstrates improved efficiency of filtration.

Suitable water soluble salts may be metal salts, for example an alkali metal salt, such as sodium, lithium or potassium; or an ammonium salt or an organic amine salt such as methylamine or TRIS (tris(hydroxymethyl)aminomethane) salt. Preferred salts are the sodium salt, potassium and ammonium salts. A further preferred salt is the TRIS salt. Most preferred is the sodium salt.

In general, the solution of calcium chloride will be an aqueous or substantially aqueous solution. In general the solution of the water soluble salt will be an aqueous or substantially aqueous solution. By substantially aqueous solution herein, we mean a solution in water which may also contain small amounts of organic or inorganic compounds, for

example arising from incomplete removal of solvent after the previous manufacturing stage. It will be understood that the presence of small amounts of organic or inorganic impurities may require adjustments to the process conditions as herein described (for example temperature) in order to obtain a product which can be filtered efficiently, but that any such adjustments would not require undue experimentation by the skilled man.

In general, process parameters which are features of the present invention comprise the temperature at which the two solutions are added together and the period of time for which the two solutions are mixed.

In general, the addition of the calcium chloride solution is carried out over a period of time, hereinafter referred to as the 'addition time'. After addition of the calcium chloride solution has been completed, the mixture is generally stirred for a period of time hereinafter referred to as the 'hold time'. Reference hereinbefore to mixing of the calcium chloride solution with the water-soluble salt solution for a period of time is to be understood to refer to mixing these solutions for the combination of the addition time and the hold time.

In one embodiment, the addition is carried out at a temperature (hereinafter referred to as 'the addition temperature') of between 30 and approximately 45°C, preferably between 32 and 43°Cand most preferably at approximately 40°C.

In one embodiment of the invention the addition time is 5 to 60 minutes, in particular 15-30 minutes.

In one embodiment, the hold time is at least 10 minutes. In particular, the hold time is at least 30 minutes. It is convenient to stir the mixture during the hold time at approximately the temperature of addition.

Therefore in one aspect of the invention, the addition temperature, addition time and hold time are selected to give a product which demonstrates improved efficiency of filtration.

Therefore in one aspect, the present invention provides a process for the manufacture of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid calcium salt, which process comprises mixing of a solution of calcium chloride with a solution of a water-soluble salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid under conditions such that the addition temperature, addition time and hold time (all as hereinbefore defined) are selected to give a product which demonstrates improved efficiency of filtration.

In particular, the calcium chloride is added at a temperature of between 32 and 43°C over a period of 15 to 30 minutes, the mixture held at a temperature of between 32 and 43°C over a period of at least 30 minutes, then the product is isolated by filtration and then dried.

In a further aspect of the invention, the addition temperature and hold time are selected to give a product which demonstrates improved efficiency of filtration.

In particular, the addition temperature is 32 to 43°C and the hold time is at least 30 minutes.

In a further aspect of the invention, the addition temperature is selected to give a product which demonstrates improved efficiency of filtration. In particular, the addition temperature is 32 to 43°C.

As previously mentioned, the process of the invention results in a more efficient filtration process such that the solid product isolated on the filter has a reduced water content (and therefore higher 'paste strength') than the equivalent product obtained after precipitation at 20°C. Typically, the paste strengths obtained with the process of the present invention will be greater than 40% w/w. As a consequence of increased paste strength, the final drying step after removal from the filter may be of shorter duration and hence manufacturing output may increase.

Therefore a further aspect of the invention provides a product obtainable by the process of the present invention.

Another aspect of the invention provides a product obtained by the process of the present invention.

Another aspect of the invention provides a product of the process of the present invention, isolated on a filter with a paste strength of greater than 40%w/w. It will be understood that the term 'paste strength' is defined as the %w/w of the product compound in the isolated solid product (with the balance consisting of water).

Suitable conditions for isolating the product include pressure filter or centrifuge. The product can be dried in a pressure filter or centrifuge under nitrogen flow or by vacuum or discharged from the isolation equipment into a cone drier, for example, and dried under vacuum.

The observed improved efficiency of filtration, as described hereinbefore, which is achieved with the process of the invention, may result from the solid product obtained possessing different physical form to that achieved by the process described in the prior art. This different physical form is provided as a further aspect of the invention. It is to be

understood that the solid product obtained both from the inventive process and from the prior art process as described, is amorphous and thus any difference in physical form arising from the inventive process is not due to crystallinity.

It may be that the different physical form is manifested by an increased particle size of the product arising from the inventive process. The particle size may be illustrated for example by measurement of the specific surface area of the solid.

A preferred aspect of the present invention provides a process comprising mixing of a solution of calcium chloride with a solution of a water-soluble salt of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid such that the addition temperature, addition time and hold time are adjusted to give a product with a specific surface area such that filtration, washing and drying of the isolated product are optimally efficient.

The invention is further illustrated, but not limited by the following examples.

Example 1

Preparation of the solutions used in the experiments which generated the data presented in Example 2 below was carried out as follows.

(*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid methylamine salt, 2M sodium hydroxide solution and water were mixed together, the solution evaporated to low volume under vacuum at <40°C to remove methylamine and then made up to a standard volume with water. Aliquots of the stock solutions were taken and calcium salt precipitated by dropwise addition of a solution of calcium chloride in water using the conditions (temperature, addition time, hold time and agitation rate) according to the experimental design. The reaction mixture was then cooled to 20°C, filtered, washed with three portions of water and deliquored for a standard time before measuring the paste strength of the isolated material.

Example 2

Data

The data presented below illustrate the improvement in paste strength associated with temperature, addition time and hold time. The data were generated during experiments

carried out as part of a factorial experimental design using essentially the process described in Example 1.

Experiment ID #	NaOH (eq)	Agitation (rpm)	Temp (°C)	Addition time (mins)	Hold time (mins)	Paste Strength (%w/w)
1	0.99	550	32	15	10	41.4%
2	0.93	550	40	15	10	55.9%
3	0.96	400	36	6	10	42.7%
4	0.99	550	40	0	10	48.7%
5	0.99	550	40	15	30	62.9%
6	0.96	400	36	6	10	42.4%
7	0.93	250	32	0	30	40.5%
8	0.99	250	32	15	30	39.5%
9	0.96	400	36	6	10	43.3%
10	0.99	250	40	15	10	53.9%
11	0.93	550	32	0	10	34.8%
12	0.93	250	40	0	10	53.9%
13	0.93	550	32	15	30	51.6%
14	0.99	250	40	0	30	60.7%
15	0.93	250	32	15	10	42.9%
16	0.93	250	40	15	30	62.0%
17	0.99	550	32	0	30	37.0%
18	0.99	250	32	0	10	29.1%
19	0.96	400	36	6	10	42.9%
20	0.93	550	40	0	30	64.6%

Example 3

Comparative experiment carried out at 20°C

Sodium hydroxide (8% w/w aqueous solution; 33.4 ml) was added to a stirred mixture of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid methylammonium salt (37.7 g) in degassed water (310 ml) at 20°C and the mixture was stirred for one hour. The mixture was filtered and a solution of calcium chloride dihydrate (6.5 g) in water (37.7 ml) was added dropwise at 20°C over 20 minutes. The mixture was stirred for 30 minutes and the resultant solid filtered. The solid

was washed with water (339 ml) and dried under a flow of nitrogen to give non-crystalline calcium salt of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid with a paste strength of 22.2% prior to drying.

CLAIMS

1. A process for the manufacture of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, which process comprises mixing of a solution of calcium chloride with a solution of a water-soluble salt of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid, wherein the process parameters are selected to give a product which demonstrates improved efficiency of filtration.

2. A process according to claim 1 comprising mixing of a solution of calcium chloride with a solution of a water-soluble salt of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid such that the addition temperature, addition time and hold time (all as hereinbefore defined) are selected to give a product which demonstrates improved efficiency of filtration.

3. A process according to any preceding claim wherein the addition temperature, addition time and hold time are adjusted to give a product with a specific surface area such that filtration, washing and drying of the isolated product are optimally efficient.

4. A process according to any preceding claim wherein the addition temperature is 32-43°C.

5. A process according to any preceding claim wherein the hold time is at least 30 minutes.

6. A process according to any preceding claim wherein the water soluble salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid is an alkali metal salt, an ammonium salt or an organic amine salt.

7. A process according to any preceding claim wherein the water soluble salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid is an alkali metal salt.

8. A process according to any preceding claim wherein the water soluble salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid is the sodium salt.